Appendix A
Pending Claims

Claim 1 (original): A compound that binds to an mpl receptor comprising the structure

TMP_1-$(L_1)_n$-TMP_2

wherein TMP_1 and TMP_2 are each independently selected from the group of core compounds comprising the structure:

X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10},

wherein,

X_2 is selected from the group consisting of Glu, Asp, Lys, and Val;
X_3 is selected from the group consisting of Gly and Ala;
X_4 is Pro;
X_5 is selected from the group consisting of Thr and Ser;
X_6 is selected from the group consisting of Leu, Ile, Val, Ala, and Phe;
X_7 is selected from the group consisting of Arg and Lys;
X_8 is selected from the group consisting of Gln, Asn, and Glu;
X_9 is selected from the group consisting of Trp, Tyr, and Phe;
X_{10} is selected from the group consisting of Leu, Ile, Val, Ala, Phe, Met, and Lys;
L_1 is a linker; and
n is 0 or 1;

and physiologically acceptable salts thereof.

Claim 2 (original): The compound according to Claim 1 wherein said TMP_1 and TMP_2 are independently selected form the group consisting of:

X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11};
X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12};
X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13};
X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}-X_{14};
X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10};
X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11};
X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12};
X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}; and
X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}-X_{14},

wherein X_2 - X_{10} are as defined;

X_1 is selected from the group consisting of Ile, Ala, Val, Leu, Ser, and Arg;
X_{11} is selected from the group consisting of Ala, Ile, Val, Leu, Phe, Ser, Thr, Lys, His, and Glu;
X_{12} is selected from the group consisting of Ala, Ile, Val, Leu, Phe, Gly, Ser, and Gln;

X_{13} is selected from the group consisting of Arg, Lys, Thr, Val, Asn, Gln, and Gly; and

X_{14} is selected from the group consisting of Ala, Ile, Val, Leu, Phe, Thr, Arg, Glu, and Gly.

Claim 3 (withdrawn): The compound according to Claim 1 wherein said TMP_1 and/or TMP_2 are derivatized as set forth in one or more of the following:

one or more of the peptidyl [-C(O)NR-] linkages (bonds) have been replaced by a non-peptidyl linkage such as a -CH_2-carbamate linkage [-CH_2-OC(O)NR-]; a phosphonate linkage; a -CH_2-sulfonamide [-CH_2-$S(O)_2$NR-] linkage; a urea [-NHC(O)NH-] linkage; a -CH_2-secondary amine linkage; or an alkylated peptidyl linkage [-C(O)NR^6- where R^6 is lower alkyl];

the N-terminus is a -NRR^1 group; to a -NRC(O)R group; to a -NRC(O)OR group; to a -$NRS(O)_2$R group; to a -NHC(O)NHR group where R and R^1 are hydrogen and lower alkyl with the proviso that R and R^1 are not both hydrogen; to a succinimide group; to a benzyloxycarbonyl-NH- (CBZ-NH-) group; or to a benzyloxycarbonyl-NH- group having from 1 to 3 substituents on the phenyl ring selected from the group consisting of lower alkyl, lower alkoxy, chloro, and bromo;

the C terminus is -$C(O)R^2$ where R^2 is selected from the group consisting of lower alkoxy and -NR^3R^4 where R^3 and R^4 are independently selected from the group consisting of hydrogen and lower alkyl.

Claim 4 (withdrawn): The compound according to Claim 1 wherein all of the amino acids have a D configuration.

Claim 5 (withdrawn): The compound according to Claim 1 wherein at least one of the amino acids has a D configuration.

Claim 6 (withdrawn): The compound according to Claim 1 which is cyclic.

Claim 7 (original): The compound according to Claim 1 wherein TMP_1 and TMP_2 are each

Ile-Glu-Gly-Pro-Thr-Leu-Arg-Gln-Trp-Leu-Ala-Ala-Arg-Ala. (SEQ ID NO: 1).

Claim 8 (withdrawn): The compound according to Claim 1 wherein L_1 comprises a peptide.

Claim 9 (withdrawn): The compound according to Claim 8 wherein L_1 comprises Y_n, wherein Y is a naturally-occurring amino acid or a stereoisomer thereof and n is 1 through 20.

Claim 10 (withdrawn): The compound according to Claim 8 wherein L_1 comprises $(Gly)_n$, wherein n is 1 through 20, and when n is greater than 1, up to half of the Gly residues may be substituted by another amino acid selected from the remaining 19 natural amino acids or a stereoisomer thereof.

Claim 11 (withdrawn): The compound according to Claim 8 wherein L_1 is selected from the group consisting of

$(Gly)_3Lys(Gly)_4$ (SEQ ID NO: 6);
$(Gly)_3AsnGlySer(Gly)_2$ (SEQ ID NO: 7);
$(Gly)_3Cys(Gly)_4$ (SEQ ID NO: 8); and
GlyProAsnGly (SEQ ID NO: 9).

Claim 12 (withdrawn): The compound according to Claim 8 wherein L_1 comprises a Cys residue.

Claim 13 (withdrawn): A dimer of the compound according to Claim 12.

Claim 14 (withdrawn): The dimer according to claim 13 which is

TMP_1-Gly_3-Cys-Gly_4-TMP_2
|
TMP_1-Gly_3-Cys-Gly_4-TMP_2.

Claim 15 (withdrawn): 15. The compound according to Claim 1 wherein L_1 comprises $(CH_2)_n$, wherein n is 1 through 20.

Claim 16 (original) The compound according to Claim 1, which is selected from the group consisting of

IEGPTLRQWLAARA-GPNG-IEGPTLRQWLAARA (SEQ. ID NO: 10)

IEGPTLRQCLAARA-GGGGGGGG-IEGPTLRQCLAARA (cyclic)
|_____| (SEQ. ID NO: 11)

IEGPTLRQCLAARA-GGGGGGGG-IEGPTLRQCLAARA (linear)
(SEQ. ID NO: 12)

IEGPTLRQALAARA-GGGGGGGG-IEGPTLRQALAARA (SEQ. ID NO: 13)

IEGPTLRQWLAARA-GGGKGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 14)

IEGPTLRQWLAARA-GGGK(BrAc)GGGG-IEGPTLRQWLAARA
(SEQ. ID NO: 15)

IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 16)

IEGPTLRQWLAARA-GGGK(PEG)GGGG-IEGPTLRQWLAARA
(SEQ. ID NO: 17)

IEGPTLRQWLAARA-GGGC(PEG)GGGG-IEGPTLRQWLAARA

(SEQ. ID NO: 18)

IEGPTLRQWLAARA-GGGNGSGG-IEGPTLRQWLAARA (SEQ. ID NO: 19)

IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA
|
IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 20);

IEGPTLRQWLAARA-GGGGGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 21).

Claim 17 (withdrawn): The compound according to Claim 1 or 2, which has the formula

$(Fc)_m$-$(L_2)_q$-TMP_1-$(L_1)_n$-TMP_2-$(L_3)_r$-$(Fc)_p$

wherein L_1, L_2 and L_3 are linker groups which are each independently selected from the linker groups consisting of

Y_n, wherein Y is a naturally-occurring amino acid or a stereoisomer thereof and n is 1 through 20;

$(Gly)_n$, wherein n is 1 through 20, and when n is greater than 1, up to half of the Gly residues may be substituted by another amino acid selected from the remaining 19 natural amino acids or a stereoisomer thereof;

$(Gly)_3Lys(Gly)_4$ (SEQ ID NO: 6);

$(Gly)_3AsnGlySer(Gly)_2$ (SEQ ID NO: 7);

$(Gly)_3Cys(Gly)_4$ (SEQ ID NO: 8);

GlyProAsnGly (SEQ ID NO: 9);

a Cys residue; and

$(CH_2)_n$, wherein n is 1 through 20

Fc is an Fc region of an immunoglobulin; m, p, q and r are each independently selected from the group consisting of 0 and 1, wherein at least one of m or p is 1, and further wherein if m is 0 then q is 0, and if p is 0, then r is 0; and physiologically acceptable salts thereof.

Claim 18 (withdrawn): The compound according to Claim 17 wherein L_1, L_2 and L_3 are each independently selected from the group consisting of Y_n, wherein Y is selected a naturally-occurring amino acid or a stereoisomer thereof and n is 1 through 20.

Claim 19 (withdrawn): The compound according to Claim 18 wherein L_1 comprises $(Gly)_n$, wherein n is 1 through 20, and when n is greater than 1, up to half of the Gly residues may be

substituted by another amino acid selected from the remaining 19 natural amino acids or a stereoisomer thereof.

Claim 20 (withdrawn): The compound according to Claim 18 wherein L_1, L_2 and L_3 are independently selected from the group consisting of

$(Gly)_3Lys(Gly)_4$ (SEQ ID NO: 6);
$(Gly)_3AsnGlySer(Gly)_2$ (SEQ ID NO: 7);
$(Gly)_3Cys(Gly)_4$ (SEQ ID NO: 8); and
GlyProAsnGly (SEQ ID NO: 9).

Claim 21 (withdrawn): The compound according to Claim 18 wherein L_1, L_2, or L_3 comprises a Cys residue.

Claim 22 (withdrawn): A dimer of the compound according to Claim 21.

Claim 23 (withdrawn): The compound according to Claim 17 wherein L_1, L_2 or L_3 comprises $(CH_2)_n$, wherein n is 1 through 20.

Claim 24 (original): A compound that binds to an mpl receptor, which is selected from the group consisting of

Fc-IEGPTLRQWLAARA-GPNG-IEGPTLRQWLAARA (SEQ. ID NO: 22)

Fc-IEGPTLRQWLAARA-GPNG-IEGPTLRQWLAARA-Fc (SEQ. ID NO: 23)

IEGPTLRQWLAARA-GGGGGGGG-IEGPTLRQWLAARA-Fc (SEQ. ID NO: 24)

Fc-GG-IEGPTLRQWLAARA-GPNG-IEGPTLRQWLAARA (SEQ. ID NO: 25)

Fc-IEGPTLRQWLAARA-GGGGGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 26)

Fc-IEGPTLRQCLAARA-GGGGGGGG-IEGPTLRQCLAARA (cyclic)
|_____| (SEQ. ID NO: 27)

Fc-IEGPTLRQCLAARA-GGGGGGGG-IEGPTLRQCLAARA (linear) (SEQ. ID NO: 28)

Fc-IEGPTLRQALAARA-GGGGGGGG-IEGPTLRQALAARA (SEQ. ID NO: 29)

Fc-IEGPTLRQWLAARA-GGGKGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 30)

Fc-IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 31)

Fc-IEGPTLRQWLAARA-GGGNGSGG-IEGPTLRQWLAARA (SEQ. ID NO: 32)

Fc-IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA

Fc-IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 33)

Fc-GGGGG-IEGPTLRQWLAARA-GGGGGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 34);

and physiologically acceptable salts thereof.

Claim 25 (withdrawn): A method of increasing megakaryocytes or platelets in a patient in need thereof, which comprises administering to said patient an effective amount of a compound according to Claim 1.

Claim 26 (withdrawn): The method according to Claim 25, wherein said amount is from 1 μg/kg to 100 mg/kg.

Claim 27 (original): A pharmaceutical composition comprising a compound according to Claim 1 in admixture with a pharmaceutically acceptable carrier thereof.

Claim 28 (withdrawn): A polynucleotide that encodes a compound according to claim 8.

Claim 29 (withdrawn): A polynucleotide that encodes a compound according to claim 13.

Claim 30 (withdrawn): A polynucleotide that encodes a compound according to claim 18.

Claim 31 (withdrawn): A polynucleotide that encodes a compound according to claim 22.

Claim 32 (withdrawn): A vector that comprises a polynucleotide according to any of claims 28-31.

Claim 33 (withdrawn): A host cell that comprises a vector according to claim 32.

Claim 34 (withdrawn): A method of producing a compound according to claims 8, 13, 18 or 22, which comprises growing a host cell according to claim 33 in a suitable nutrient medium and isolating said compound from said cell or nutrient medium.